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13. ABSTRACT (Maximum 200 words) The present study is designed to examine the relationships between hyperinsulinemia, insulin like growth factor-1, central adiposity, maximal adult weight, physical fitness and breast cancer risk in post-menopausal African-American women. The research design is a case-control study of women 55 to 79 years of age. Eligibility criteria for the cases will be newly histologically confirmed primary breast cancer. Both cases and controls will be identified during the same time-frame and will come from the same population base. None of the controls will have any previous history of malignant or gynecological conditions that may have the same risk factors in breast cancer. Plasma levels of IGF-1 and insulin will be measured by radioimmunoassay. Central adiposity will be measured as waist-to-hip ratios (WHR). Multiple logistic regression will be used to determine age adjusted odds ratios for tertiles of waist, hip, WHR, maximal adult weight gain and levels of physical activity. Corresponding 95 percent confidence intervals will be based on the logistic regression models.				
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FOREWORD

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Sanjay N. Aggarwal - Collins 9/14/98
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INTRODUCTION

Background

Many case-control studies have shown positive relationships between obesity and breast cancer risk in postmenopausal women (1-3). Obesity is often measured using body mass index (BMI). However, some researchers believe that BMI may not be the best predictor of postmenopausal breast cancer risk (4-6). Several studies suggest that pattern of body fat distribution is more important than overall measures of obesity (7-9). Ballard-Barbash (9) showed that central to peripheral body fat distribution predicted breast cancer risk independently of the degrees of adiposity. Other studies have used waist-to-hip ratios (WHR) to measure central adiposity. A study of postmenopausal Iowa women aged 55-69 years found that the older, heavier women showed a positive association between WHR and risk for breast cancer (8). Schapira et al. (7) also showed that women with predominantly upper body obesity were significantly at greater risk for breast cancer. However, Sellers et al. (10) showed that the association of WHR with the risk for breast cancer was found predominately with women who had a family history of breast cancer.

The relationship between obesity and breast cancer is associated with increased estrogen levels. It has been shown that the greater the body fatness (BMI) the greater the bioavailability of estradiol (11). Obesity is also associated with some degree of insulin resistance and hyperinsulinemia. Hyperinsulinemia, known as a risk factor for the development of diabetes, has recently been suggested to be a risk factor for breast cancer. A case-control study of 223 European women with breast cancer found that hyperinsulinemia with insulin resistance was a significant marker of increased breast cancer risk (12). Insulin's tumor growth promoting effect *in vivo* is believed to be through Type I insulin-like growth factor (IGF-1). Adipose tissue synthesizes significant levels of IGF-1 under the control of insulin (13). Insulin and IGF-1 were found to be potent mitogens for the stimulation of the growth of MCF-7 human breast cancer cells with the presence of estrogen (14-16). Peyrat (17) found IGF-1 to be significantly higher in a population of primary breast cancers than in the controls and that IGF-1 concentrations were greater in patients over 50 years of age than in those between 35 and 50.

IGF-1 has been shown to bind to its membrane receptors (IGF-1 receptors) by competitive binding and cross-linking techniques in cultured breast cancer cell lines (16,18). IGF-1 receptor concentrations are higher in breast tumors than in benign breast disease and that IGF-1 and IGF-1 receptors appear to be positively correlated to both estrogen and progesterone receptors in patients with breast cancer (19,20). Women with breast cancer tend to have a greater circulating, non-protein bound and albumin bound estradiol. Researchers have shown synergism between estradiol and IGF in stimulating the growth of human breast cancer cell line (14,21). It is believed that estrogen modulates the production of IGF-1. However, the mechanisms by which IGF-1 and IGF-1 receptors are regulated in breast cancer are not understood (19,22).

Levels of IGF-1 from adipose tissue may be important in regulating tumor growth. Available estradiol is positively related to insulin, IGF-1, and adiposity. This evidence suggests that obesity and excess insulin expressed through IGF-1 production are risk factors for breast cancer. However, these studies consisted of virtually all white populations and therefore, needs to be confirmed in other populations.

Several studies have shown physical activity to have a protective effect against breast cancer risk (23-27). This decreased risk of breast cancer was found in not only athletes, but women who had physically high activity jobs and who had higher energy expenditure(25-27). The mechanism through which physical activity modifies breast cancer risk is thought to be through a hormone related pathway (26). Persons who are physically active show a reduction in body fatness, improved glycemic control, improved insulin sensitivity, and a reduction in fasting hyperinsulinemia (28). A possible mechanism for the protective effect of physical activity may be through decreased hyperinsulinemia and IGF-1.

This research is innovative because very few studies examining the relationship between hyperinsulinemia and IGF-I with breast cancer risk were conducted in human subjects. Also, no other study has looked at whether increased levels of IGF-1 may be related to central adiposity and whether physical activity could reduce levels of IGF-1. The relationship between physical activity and breast cancer risk may have a metabolic/endocrine tie with hyperinsulinemia and IGF-1.

Friedenreich and Rohan (29) reported that the time period for the effect of physical activity on breast cancer risk has not been determined. We plan to examine whether women who are physically active have a protective effect for breast cancer risk and if so what time period is associated with this decrease risk. Therefore, a surrogate measure of energy balance using physical activity and weight during specific periods of hormonal change such as menarche, pregnancy, and menopause will be developed.

The significance in understanding the relationships between these endocrine factors in the development of breast cancer is extremely important in helping to better understand and prevent this disease. More information is needed on the association of physical activity and postmenopausal breast cancer and understanding how obesity influences the risk for postmenopausal breast cancer.

Obesity is a major public health problem in the US, especially among African American women ages 40-60 years. African American women have a two-fold increased risk of obesity compared to their white counterparts (30) and African Americans over the age of 65 have been diagnosed with non-insulin diabetes mellitus nearly three times as much as whites of similar age, resulting in high circulating levels of insulin. Moreover, the mortality rate from breast cancer is much higher in African-American women when compared to the U.S. population. Since 1974, survival rates for whites have increased, whereas the survival for blacks showed no change and remains poor relative to that for whites, with a 5-year survival of only 62% compared with 80% for whites (31).

We believe that the incidence and mortality from postmenopausal breast cancer can be reduced by reducing the prevalence of obesity and increased physical activity. Also, possible biological markers for breast cancer risk may be hyperinsulinemia and IGF-1. Waist-to-hip ratios will be our measure for central adiposity because it is considered a more stable measure than BMI and is closely correlated with some of the metabolic consequences (hyperinsulinemia, IGF-1) of excess adiposity. We will also examine the relationship between maximal adult weight gain during specific periods of hormonal change with risk for developing breast cancer. It is believed that there is an increased risk associated with heavier weight both during menopause and at the time of breast cancer diagnosis (32,33).

The proposed research is innovative because it is the only study that plans to examine

central adiposity, maximal adult weight gain, physical activity, hyperinsulinemia, IGF-I and their relationships to postmenopausal breast cancer among African American women. Very few studies have examined the relationship between hyperinsulinemia, IGF-I in actual breast cancer patients. The majority of the research studies used in-vitro models. Controlling obesity and hyperinsulinemia and increasing physical activity may be important in the prevention and treatment of postmenopausal breast cancer.

Hypotheses/Purpose

The present study is designed to examine the relationships between central obesity, physical activity, hyperinsulinemia, IGF-1, and breast cancer in post-menopausal African-American women. Specifically, this research is expected to show that central obesity is positively associated with increased levels of insulin, IGF-1 and risk for breast cancer. Additionally, we expect to show that increased levels of IGF-1 and maximal adult weight gain are positively associated with the risk for developing breast cancer and determine the time period for the protective effect of physical activity on breast cancer risk.

BODY

Research methods

Laboratory Analysis

Plasma samples are drawn into tubes containing ethylene-diaminetetraacetic acid (EDTA). The plasma is separated by centrifugation and analyzed immediately. Laboratory analysis is performed by a commercial laboratory using methods approved by the Food and Drug Administration, with proficiency testing using the College of American Pathologist samples. Insulin levels are measured by radioimmunoassay (RIA). IGF-1 is measured using a RIA procedure suggested by the National Institute for Diabetes, Digestive and Kidney Diseases (NIDDK) (34).

Questionnaires

Data is collected using a questionnaire that includes questions on basic demographic and lifestyle data, family and medical history, and reproductive and menstrual history. Specific questions to determine weight gained and levels of physical activity during menarche, pregnancy, and menopause are ascertained. The Historical Physical Activity Survey which is being used to determine levels of physical activity.

Anthropometric Measurement

Weight is measured in street clothes, without shoes, using a balanced beam scale. Height is measured without shoes using a portable stadiometer. The patient is instructed to stand erect with feet together and shoulder blades in contact with the vertical surface of the stadiometer. The moveable headboard is lowered carefully until it touches the crown of the head. Height is recorded to the nearest 1/4 inch.

When taking waist-to-hip ratios, patients are asked to wear light clothing to ensure that the tape

is correctly positioned. Patients stand erect with the abdomen relaxed, arms at their side, feet together and with their weight equally divided over both legs. Waist circumference is measured by facing the subject and placing an inelastic tape around the subject in a horizontal plane, at the level of the natural waist which is the narrowest part of the torso. If the narrowest point could not be found, the tape was applied horizontally midway between the lowest rib margin and the iliac crest. Hip circumference is measured at the point yielding the maximum circumference over the buttocks with the tape held in a horizontal plan, Measurements are taken to the nearest 1/2cm. Questionnaires and anthropometric measurements are performed by a trained technician.

Recruitment

Recruitment of cases and controls is done through the Howard University (HU) Mammography Screening Clinic and through the HU Breast Clinic. Howard University Hospital physicians (i.e. oncologist and radiologist) are contacted to discuss the study goals and to ask for their participation in identifying patients who are eligible for the study. Brochures and flyers outlining the study goals, eligibility criteria and exclusion criteria are distributed to physicians and nurses who work with oncology patients. The PI works closely with the oncologist to assist with recruitment efforts. The research associate interfaces daily with the clinic to identify eligible patients through the oncologist and/or nurses. The controls will consist of women who received and had a normal mammography within the past three months. The women who agree to participate in the study will be given a clinic appointment. During the clinic appointment the research associate obtains their consent to participate in the study, anthropometric measurements and serum collection. Also, study controls are recruited prospectively as they come for mammography screening. Recruitment of cases will be solely based on physician referrals. The cases are women with newly histologically confirmed primary breast cancer who are referred by the oncologist. Cases will be identified and recruited prospectively. Those patients who had a positive biopsy within the past three months are also eligible to participate. Once the patient has agreed to participate in the study, the research associate will give them a clinic appointment to obtain study measurements.

Inclusion and Exclusion Criteria

Cases enter the study before being diagnosed with breast cancer and therefore, would not be treated with adjuvant hormonal or chemotherapy. Inclusion criteria for the cases are newly histologically confirmed primary breast cancer identified via biopsy at the Howard University Hospital. Both cases and controls are identified during the same time frame and are from the same population-base. None of the controls have any previous history of malignant or gynecological conditions that may have the same risk factors in breast cancer. Exclusion criteria for both cases and controls includes: (1) engaging in a dietary or therapeutic regimen for weight reduction during the year preceding the study; (2) reporting a weight loss of over 10% of usual weight in the 3 months preceding the study; (3) having undergone a hysterectomy or ovariectomy; and (4) having a medical condition that restricted the collection of anthropometric measurements. Persons with comorbid conditions such as diabetes mellitus (Type I and II), polycystic ovary syndrome, manifest thyroid or adrenal dysfunction, and endocrine therapy are excluded from participating in the study. Additional exclusion criteria are individuals treated with adjuvant hormonal or chemotherapy (ie. tamoxifen, progestin, estrogen replacement therapy), synthetic retinoid fenretinide, glucocorticoid, and

alcoholism.

Results and Discussion

Hiring of Personnel

After the grant was awarded August 15, 1997, the two positions along with the position descriptions for medical research assistant and data manager were approved by the University in October 1997. The positions were advertised and potential candidates were interviewed in November and December 1997. Two persons were selected and started working on the project in January and February 1998. In February, they were trained regarding study goals, objectives, protocols, responsibilities and how to finalize study questionnaires. Patient recruitment began late February 1998.

Sample size

The research design is a case-control study of postmenopausal women who are 55 to 79 years of age. Initially, the sample size in the proposal was 50 cases and 50 control. However, after the revised budget was submitted, DOD asked me to respond to the study weakness cited by the reviewers. One of the cited study weakness was that the sample size was too small to detect a difference. In response to the reviewer's critic, the sample size was increased from 100 to 244 subjects. The increase is based on 80% power, $\alpha=0.05$ and a relative risk of 2.0 for 122 cases and 122 controls (35). However, the original grant proposal and revised budget does not reflect this increase in sample size.

Patient Recruitment

Recruitment of patients has taken place at the Howard University Mammography clinic. A prescreening questionnaire was developed and administered to potential participants to determine initial eligibility. After the patients met the prescreening criteria, they are given an appointment to determine final screening criteria. Once the patients are eligible, they participate in a (1) one hour data collection interview. After collection, serum samples are sent to Quest Diagnostics, Inc., a commercial laboratory for analysis. Patient recruitment and analysis is ongoing.

Since February 1998 through August 15, 1998 (6 months), we have recruited 85 postmenopausal women without breast cancer who are serving as the control subjects and 7 postmenopausal women with breast cancer. We are very pleased with the number of patients enrolled in the study (92) within the first 6 months of recruiting. Our goal is to recruit 122 patients a year for two years. However, we are anticipating that the recruitment of women with breast cancer maybe somewhat slow. There are several reasons for this. First, the recruitment criteria eliminates persons who are diabetic and who are taking estrogen replacement therapy since the study is measuring insulin-like growth factor type-1 (IGF-1) and estradiol. In the African-American population, the prevalence of non-insulin dependent diabetes is very high among women. Secondly, it is becoming increasingly difficult to find postmenopausal women who are not taking some form of estrogen replacement therapy. Also, we are finding a larger number of premenopausal black women who are developing breast cancer instead of postmenopausal black women at our institution. Therefore,

expanding the recruitment data base to include additional sites to recruit patients for the study will be essential. In May 1998, I submitted a grant proposal to the Georgetown Medical Center's Institutional Review Boards to recruit African American postmenopausal breast cancer patients who meet the study criteria for this project. The proposal was approved in July 1998. I am currently collaborating with Dr. Kevin Cullen who is a medical oncologist at the Lombardi Research Center. Thus, with the addition of another site, we should be able to increase the number of breast cancer patients within the time frame allocated for this project.

CONCLUSIONS

Presently, data collection is on target, with 92 subjects recruited within 6 months. We are anticipating slow recruitment for postmenopausal African-American women with breast cancer. This is a direct result of our exclusion criteria of women with NIDDM and taking estrogen replacement therapy. However, we are taking the necessary steps to broaden our recruitment efforts to include Georgetown University Medical Center. Recruitment at this medical center will start in October 1998. Overall, the research staff are doing an outstanding job with data collection.

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